PATENT SPECIFICATION

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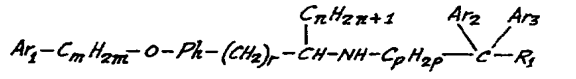
(19)

(54) 1-(ARALKOXYPHENYL)-2- OR -3-(BIS-ARYLALKYLAMINO)-ALKANES, PROCESS FOR THEIR MANUFACTURE AND PHARMACEUTICAL PREPARATIONS CONTAINING THEM

(71) We, CIBA-GEIGY AG, a body corporate organised according to the laws of Switzerland, of Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to 1-(aralkoxyphenyl)-2 or 3-(bis-arylalkylamino)-alkanes and a process for their manufacture.

The present invention provides 1-(aralkoxyphenyl)-2 or 3-(bis-arylalkylamino)-alkanes of the general formula I



(I)

wherein Ar_1, Ar_2 and Ar_3, which may be the same or different, each represents an unsubstituted phenyl radical or a phenyl radical substituted by one or more substituents selected from halogen atoms and lower alkyl, lower alkoxy, trifluoromethyl, nitro, amino, mono-lower alkylamino, di-lower alkylamino, lower alkanoylamino, cyano, carboxy, carbo-lower alkoxy, carbamoyl, aminomethyl, mono-lower alkylaminomethyl and di-lower alkylaminomethyl groups, Ph represents an unsubstituted phenylyene radical or a phenylene radical substituted by one of the substituents listed for Ar_1, n is 0 or an integer from 1 to 4, m and p, which may be the same or different, each represents an integer from 1 to 4, r is the integer 1 or 2, and R_1 represents a hydrogen atom or a hydroxy group. The invention also provides salts of these compounds.

Of the phenyl radicals Ar_1 preferably represents a phenyl radical substituted by up to five, advantageously one or two substituents selected from lower alkyl groups, e.g. methyl, ethyl, *n*- and *i*-propyl and -butyl groups; lower alkoxy groups, e.g. methoxy, ethoxy, n- and i-propoxy and -butoxy groups; halogen atoms, e.g. fluorine, chlorine and bromine atoms; trifluoromethyl; nitro; amino; mono- and di-lower alkylamino, e.g. mono- and dimethylamino, mono- and diethylamino; lower alkanoylamino, e.g. acetylamino, and propionylamino; cyano; carboxy; carbo-lower alkoxy, e.g. carbomethoxy and carbethoxy; carbamoyl; aminomethyl; mono- and di-lower alkylaminomethyl, e.g. mono- and dimethylaminomethyl groups. Each of Ar_2 and Ar_3 is preferably an unsubstituted phenyl radical or a phenyl radical substituted by one substituent selected from those given above for Ar_1.

The term "lower", referred to above or hereinafter in connection with organic radicals or compounds respectively, defines those having up to 4, preferably up to 3, and advantageously one or two, carbon atoms.

The phenylene radical Ph is preferably an unsubstituted 1,4-phenylene radical but may be a 1,2- or 1,3-phenylene radical, or such a phenylene radical substituted by one substituent selected from halogen atoms and lower alkyl, lower alkoxy, and

trifluoromethyl groups, e.g. those listed for Ar_1; and R_1 is preferably a hydrogen atom.

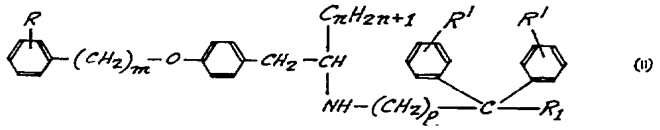
The lower alkyl group C_nH_{2n+1} is preferably a methyl group but may be any other appropriate group mentioned above. The lower alkylene group C_mH_{2m} preferably stands for $(CH_2)_m$, especially a methylene radical, but also for a 1,1- or 1,2-ethylene, 1,1-, 2,2-, 1,2- or 1,3-propylene or -butylene radical; and C_pH_{2p} preferably represents $(CH_2)_p$, especially a 1,2-ethylene radical, but also any other of the above-mentioned alkylene groups.

Salts of the compounds of formula I are preferably physiologically tolerable acid addition salts, e.g. those derived from the acids listed below.

The compounds of the invention exhibit valuable pharmacological properties, primarily hypotensive, antihypertensive and bradycardic activity. This is demonstrable in animal tests, advantageously using mammals, e.g. rats, cats or monkeys, as test objects. The animals may either be normotensive or hypertensive, e.g. genetically or adrenal regeneration hypertensive rats. The compounds of the invention can be administered enterally or parenterally, advantageously orally, or subcutaneously, intravenously, intraperitoneally or intraduodenally, for example, within gelatin capsules or in the form of starchy suspensions or aqueous solutions respectively. The dosage administered may range from 0.1 to 100 mg/kg/day, preferably from 1 to 50 mg/kg/day, advantageously from 5 to 25 mg/kg/day. The lowering effect on the blood pressure is recorded either directly by means of a catheter, for example placed in the rat's caudal artery, or indirectly by sphygmomanometry at the rat's tail, and a transducer, expressing the blood pressure prior and after dosing in mm Hg. Thus, for example, the d,l - 1 - [4 - (4 - chlorobenzyloxy) - phenyl] - 2 - (3,3 - diphenylpropylamino) - propane, a representative member of the compounds of the invention, advantageously in the form of its hydrochloride, or preferably the levorotatory antipode thereof, is very effective in hypertensive rats at *p.o.* doses as low or lower than 5 mg/kg/day and maximally about 24 hours after dosing. Antihypertensive doses cause only minor impairment of sympathetic nerve function, unlike antihypertensive agents which act by adrenergic neurone blockade, as assessed by pressor responses to electrical stimulation of the spinal cord of pithed rats. The representative compound of the invention used in the tests also differs from certain centrally acting antihypertensive agents which cause sedation. Moreover, the d,l-hydrochloride does not cause brain catecholamine-depletion, unlike the centrally acting agents, although it does cause depletion in peripheral tissues, for example, the heart. Furthermore, it does not produce sedation in monkeys at hypotensive doses, as does α-methyldopa. Accordingly, the compounds of the invention are useful antihypertensive and bradycardic agents, for example in the treatment or management of primary or secondary hypertension, or angina pectoris respectively. They are also useful intermediates in the preparation of other valuable products, especially of pharmacologically active compositions.

Particularly useful are compounds of the general formula I, in which each of Ar_1, Ar_2 and Ar_3 represents a phenyl, (lower alkyl)$_x$-phenyl, (lower alkoxy)$_x$-phenyl), (halogeno)$_x$-phenyl or (trifluoromethyl)-phenyl radical, Ph represents a 1,3- or 1,4-phenylene, (lower alkyl)-1,3- or 1,4-phenylene, (lower alkoxy)-1,3- or 1,4-phenylene, (halogeno)-1,3- or 1,4-phenylene or (trifluoromethyl)-1,3 or 1,4-phenylene radical, n is an integer from 1 to 4, each of m and p is an integer from 1 to 4, x is an integer from 1 to 5, r is the integer 1 or 2 and R_1 is a hydrogen atom or a hydroxy group, or a physiologically tolerable acid addition salt thereof.

Outstanding compounds of the invention are those of the general formula II



(II)

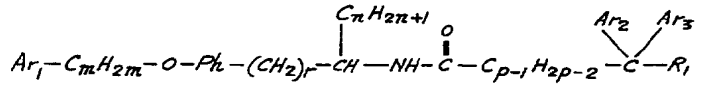
wherein each of R and R′ independently represents a hydrogen atom, a methyl or methoxy group, a fluorine, chlorine or bromine atom or a trifluoromethyl group, m, n and p each represents the integer 1 or 2, and R_1 is a hydrogen atom or a hydroxy group, and the physiologically tolerable acid addition salts thereof.

Particularly preferred are those compounds of the general formula II, wherein in R_1, m, n and p have the meanings given in the preceding paragraph, R is a chlorine atom and R′ a hydrogen atom, and the physiologically tolerable acid addition salts thereof.

Especially preferred are the compounds of the general formula II, wherein R is a chlorine atom, advantageously in the meta- or para-position, R_1 and R′ each represents a hydrogen atom, m and n both represent the integer 1 and p the integer 2, and the physiologically tolerable acid addition salts thereof.

The compounds of the invention may be prepared according to methods known per se, advantageously by:

1) reducing a compound of the general formula III



(III)

The reduction of the amide III is performed according to known methods, advantageously with a simple or complex light metal hydride, for example, a borane or an aluminium hydride, preferably an alkali metal boron or aluminium hydride, e.g. lithium aluminium hydride, sodium borohydride or a lithium or sodium tri-lower alkoxy- or bis-alkoxyalkoxy-aluminium hydride, for example, lithium tri-*t*.-butoxy- or sodium bis-(2-methoxy-ethoxy)-aluminium hydride.

The starting material may be prepared according to methods known *per se*, for example, from the corresponding phenolate, for example, an alkali metal, e.g. sodium or potassium, salt, of the phenol

$$HO—Ph—(CH_2)_r—CH(C_nH_{2n+1})—NH—CO—C_{p-1}H_{2p-2}—CH(Ar_2, Ar_3)$$

and a reactive ester of the alcohol $Ar_1—C_mH_{2m}—OH$, e.g. one of those derived from a strong inorganic or organic acid, preferably a hydrohalic, e.g. hydrochloric, -bromic or -iodic acid, or an alkane or benzene sulfonic acid, e.g. methane, *p*-toluene or *m*-bromobenzene sulfonic acid, Alternatively, an amine

$$Ar_1—C_mH_{2m}—O—Ph—(CH_2)_r—CH—(C_nH_{2n+1})—NH_2$$

can be reacted with a reactive, functional derivative of the acid

$$HOOC—C_{p-1}H_{2p-2}—CR_1(Ar_2Ar_3),$$

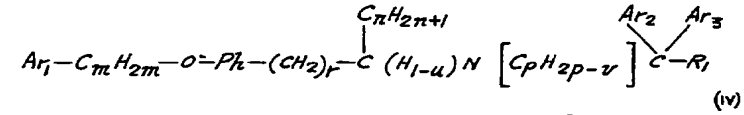
e.g. a halide or anhydride thereof. The former amines and phenols are either known or may be obtained by condensing a compound of formula

$$HO—Ph—CO—CHNH_2—C_nH_{2n+1},$$

with an acid alcohol or acid derivative respectively, in subsequent steps.

Another method for preparing a compound of the general formula I comprises

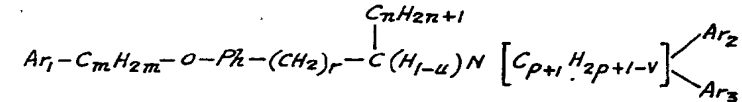
2) reducing a compound of formula IV



(IV)

wherein u is 1, v is 0 and the other symbols have the meanings given above, or u is 0, v is 1 or 3 and the other symbols have the meanings given above.

A compound in which R_1 represents a hydrogen atom is prepared by reducing a compound of formula IVa



(IVa)

wherein u is 1, v is 0 and the other symbols have the meanings given above, or u is 0, v is 1 or 3 and the other symbols have the meanings given above.

The reduction of the starting material of the formula IV or IVa may be carried out according to known methods, for example with the use of hydrogen in the presence of a catalyst, e.g. a platinum or nickel catalyst, or with nascent hydrogen, e.g.

generated electrolytically, which is advantageously used in the case of a Schiff's base IV or IVa. These compounds may also be reduced with one of the reducing agents mentioned under item 1), preferably with a simple light metal hydride, e.g. a borane.

The starting materials IV and IVa may be obtained according to methods known per se, e.g. those illustrated by the examples herein. Thus, for example, a starting material of the formula IV is obtained from the corresponding amine

$$HO—Ph—(CH_2)_r—CHNH_2—C_nH_{2n+1}$$

by condensation with the aldehyde

$$OHC—[C_{p-1}H_{2p-2-v}]CR_1Ar_2Ar_3,$$

followed by a reactive ester of an alcohol $Ar_1C_mH_{2m}—OH$.

The Schiff's base IV may also be obtained from the corresponding free or protected ketone $HO—Ph—(CH_2)_r—CO—C_nH_{2n+1}$ by condensation with an amine $H_2N[C_pH_{2p-v}]CR_1Ar_2Ar_3$ followed by a reactive ester of an alcohol $Ar_1C_mH_{2m}—OH$.

The Schiff's base IVa is obtained from the free or protected amine

$$HO—Ph—(CH_2)_r—CHNH_2—C_nH_{2n+1}$$

by condensation with the aldehyde $OHC—[C_pH_{2p-1-v}]Ar_2Ar_3$, followed by a reactive ester of an alcohol $Ar_1—C_mH_{2m}—OH$. The Schiff's base IVa may also be obtained from the corresponding free or protected ketone

$$HO—Ph—(CH_2)_r—CO—C_nH_{2n+1}$$

by condensation with an amine

$$H_2N—[C_{p+1}H_{2p+1-v}]Ar_2Ar_3,$$

followed by a reactive ester of an alcohol $Ar_1—C_mH_{2m}—OH$.

Another method for preparing the compounds of the general formula I comprises

3) condensing a compound of the general formula V

$$Ar_1—C_mH_{2m}—T \qquad (V)$$

wherein T is a reactive esterified hydroxy group, with a compound of the general Formula VI

$$HO—Ph—(CH_2)_r—CH(C_nH_{2n+1})—NH—C_pH_{2p}—CR_1(Ar_2Ar_3) \qquad (VI)$$

or a reactive salt thereof.

A reactive esterified hydroxy group is, for example, derived from a strong inorganic or organic acid, preferably a hydrohalic, e.g. hydrochloric, -bromic or -iodic acid, or an alkane or benzene sulfonic acid, e.g. methane, *p*-toluene or *m*-bromobenzene sulfonic acid.

The condensation of the starting materials V and VI is preferably carried out with the use of a reactive salt of the phenol, for example, an alkali metal, e.g. sodium or potassium salt, or in the presence of a condensing agent, and neutralizing the eliminated acid, for example, with an inorganic or organic (nitrogen) base, e.g. an alkali or alkaline earth metal carbonate or hydrogencarbonate; or tri-lower alkylamine or pyridine.

The starting materials V and VI are prepared analogously to the above starting material, e.g. from $HO—Ph—(CH_2)_r—CH(C_nH_{2n+1})NH_2$ by condensation with $U—C_pH_{2p}—CH(Ar_2Ar_3)$, wherein U is a reactive esterified hydroxy group.

The resulting compounds of the invention can be converted into each other according to known methods.

The compounds of the invention are obtained in the free form or in the form of their acid addition salts, depending on the conditions under which the process is carried out. A salt resulting can be converted into the free base in known manner, for example, with ammonia, an alkali or an ion exchanger. A resulting free base can be converted into a salt with an acid, especially one of those that are suitable for the formation of physiologically tolerable acid addition salts. Such acids are inorganic

acids, for example, mineral acids, for example, a hydrohalic, e.g. hydrochloric or hydrobromic acid; sulfuric, phosphoric, nitric and perchloric acid; and organic acids, for example aliphatic and aromatic carboxylic acids and sulfonic acids, for example formic, acetic, propionic, succinic, glycollic, lactic, malic, tartaric, citric, maleic, hydroxymaleic, pyruvic, phenylacetic, benzoic, aminobenzoic, anthranilic, 4-hydroxybenzoic, salicylic, 4-aminosalicylic, embonic, nicotinic, methanesulfonic, ethanesulfonic, hydroxyethanesulfonic, ethylenesulfonic, halobenzenesulfonic, toluenesulfonic, naphthalenesulfonic, sulfanilic and cyclohexylsulfamic acid; methionine, tryptophan, lysine and arginine, and ascorbic acid. These or other salts, for example, the picrates, can also be used in the purification of the free compounds.

In view of the close relationship between the salts and the free compounds, whenever the free compound is referred to in this specification, the reference includes a corresponding salt, provided such is possible or appropriate under the circumstances.

Resulting mixtures of isomers can be separated into the single isomers by methods in themselves known, e.g. by fractional distillation, crystallization and/or chromatography. Racemic products can likewise be resolved into the optical antipoles, for example, by separation of diastereomeric salts thereof, e.g. by the fractional crystallization of d- or l-tartrates.

The above-mentioned reactions are carried out according to standard methods, in the presence or absence of diluents, preferably such as are inert to the reagents and are solvents thereof, of catalysts, condensing or said other agents respectively and/or inert atmospheres, at low temperatures, room temperature or elevated temperatures, preferably at the boiling point of the solvents used, at atmospheric or superatmospheric pressure.

The invention further includes any variant of the present process, in which a starting material is formed *in situ* under the reaction conditions, or in which one or more of the reaction components are used in the form of their salts or optically pure antipodes.

The invention also provides pharmaceutical preparations which comprise a compound of the invention or a physiologically tolerable salt thereof as active substance in conjunction or admixture with a carrier suitable for either enteral or parenteral application. Preferred are tablets and gelatin capsules comprising the active ingredient together with a diluent, e.g. lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine, and a lubricant, e.g. silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol; for tablets also a binder, e.g. magnesium aluminium silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone, if desired, a disintegrant, e.g. starches, agar, alginic acid or its sodium salt, an enzyme of a binder, an efferverscent mixture and/or an adsorbent, a colorant, flavor and/or sweetener. Injectable compositions are preferably aqueous isotonic solutions or suspensions, and suppositories are advantageously fatty emulsions or suspensions. They may be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. They may also contain other therapeutically useful substances. The pharmaceutical preparatins are prepared according to conventional mixing, granulating or coating methods respectively and contain from 0.1 to 75% by weight, preferably from 1 to 50% by weight of the active ingredient.

The following Examples illustrate the invention. Temperatures are given in degrees Centigrade. If not specified, all evaporations are carried out under reduced pressure.

Example 1

A mixture of 210 g of 1-[4-(3-chlorobenzyloxy)-phenyl]-2-aminopropane, 158 g of β-phenylcinnamaldehyde and 1000 ml of dry benzene is stirred at reflux in an apparatus containing a water trap until no more water is collected. The solution is evaporated to dryness under reduced pressure. The residue is triturated in 1000 ml of dry tetrahydrofuran and added dropwise under nitrogen to a cooled, stirring slurry of 86.5 g of lithium aluminium hydride in 1500 ml of dry tetrahydrofuran. The whole is stirred at ambient temperature for twenty hours, then cooled and treated cautiously with saturated aqueous ammonium chloride solution until the remaining hydride has been destroyed. The mixture is filtered and the filter cake extracted with chloroform. The extract and filtrate are combined, washed with water, dried over sodium sulphate and concentrated to dryness under reduced pressure to afford a free base of the product as an oil. This material is dissolved in acetone and treated with ethereal hydrogen chloride until acidic. On cooling and adding dry ether little by little, the crystalline 1 - [4 - (3 - chlorobenzyloxy) - phenyl] - 2 - (3,3 - diphenyl-

propylamino) - propane hydrochloride is obtained. Recrystallization from methanol-ether yields analytically pure hydrochloride melting at 157—160°.

The starting material is obtained as follows: To a stirring mixture of 244 g of p-hydroxybenzaldehyde, 360 g of potassium carbonate, 32 g of potassium iodide, 1200 ml of 95% aqueous ethanol and 160 ml of water, 367 g of m-chlorobenzyl chloride are added slowly. The mixture is stirred at reflux for four hours, cooled to 80° and 2000 ml of warm water (80°) are added under stirring. The mixture is cooled and the product which forms is collected, washed with water and recrystallized from methanol to afford the desired 4-(3-chlorobenzyloxy)-benzaldehyde melting at 51—54°.

A mixture of 200 g of 4-(3-chlorobenzyloxy)-benzaldehyde, 40 g of ammonium acetate and 400 ml of nitroethane is heated under reflux for forty minutes and then allowed to cool. The precipitate which forms is collected by filtration, pressed dry and recrystallized from ethanol to yield 1-[4-(3-chlorobenzyloxy)-phenyl]-2-nitropropene melting at 110—114°. Recrystallization from ethanol raises the melting point to 117—118°, but the crude material is suitable for the next step.

To a cooled slurry of 57 g of lithium aluminium hydride in 750 ml of dry tetrahydrofuran under nitrogen, 91 g of 1-[4-(3-chlorobenzyloxy)-phenyl]-2-nitropropene in 600 ml of dry tetrahydrofuran are added dropwise. The mixture is stirred at ambient temperature for 18 hours and then cautiously, under cooling, treated dropwise with saturated aqueous ammonium chloride solution until the remaining hydride is destroyed. The mixture is filtered and the precipitate extracted with chloroform. The filtrate and extracts are combined, washed with water, dried over anhydrous sodium sulphate and concentrated to dryness under reduced pressure to afford 1-[4-(3-chlorobenzyloxy)-phenyl]-2-aminopropane as an oil, suitable for use in the next step. The hydrochloride salts melts at 152—154°.

Example 2

In a like manner, as described in Example 1, d,l - 1 - [4 - (4 - chlorobenzyloxy) - phenyl] - 2 - (3,3 - diphenylpropylamino) - propane hydrochloride, m.p. 178—180° is obtained via 4-(4-chlorobenzyloxy)-benzaldehyde, m.p. 73—75°, 1-[4-(4-chlorobenzyloxy)-phenyl]-2-nitropropene, m.p. 99—100°, and 1-[4-(4-chlorobenzyloxy)-phenyl]-2-aminopropane, the hydrochloride of the latter melts at 199—201.5°.

Example 3

To a solution of 85 g of 1-(4-hydroxyphenyl)-2-(3,3-diphenylpropylamino)-propane hydrochloride (m.p. 204—207°C, prepared from the free base which, in turn, is prepared as described by Ehrhart et al, U.S. Patent 3,152,173) in 50 ml of dimethylsulphoxide, 4.1 ml of 10 N aqueous sodium hydroxide solution are added and the whole is brought to 60° and maintained at this temperature for one hour. To this solution 4 g of 3,4-dichlorobenzyl chloride are added and the whole is stirred vigorously at ambient temperature for twenty hours. The mixture is poured into 500 ml of ice-water containing 5 ml of N aqueous sodium hydroxide solution and extracted with ethyl acetate. The organic layer is washed with saturated aqueous sodium chloride solution, dried over sodium sulphate and concentrated to dryness under reduced pressure. The residue is dissolved in a little iropropanol, treated with ethereal hydrogen chloride to acidity and refrigerated whereupon white crystals of 1 - [4 - (3,4 - dichlorobenzyloxy) - phenyl] - 2 - (3,3 - diphenylpropylamino) - propane hydrochloride are obtained, melting at 147—148°.

Example 4

When p-cyanobenzyl chloride is substituted for 3,4-dichlorobenzyl chloride of Example 3, 1 - [4 - (4 - cyanobenzyloxy) - phenyl] - 2 - (3,3 - diphenylpropylamino) - propane is obtained. Extraction of the aqueous mixture with ethyl acetate yields the free base as a white crystalline solid melting at 132—138.5°.

Example 5

A mixture of 11.9 g of 4-(4-chlorobenzyloxy)-phenylacetone, 9.8 g of 3,3-diphenyl-3-hydroxypropylamine and 100 ml of absolute ethanol is heated under reflux for one hour, cooled to room temperature and treated little by little under stirring with 6 g of sodium borohydride in 25 ml of water. The mixture is stirred for 18 hours, poured into ice-water, and the resulting precipitate collected, washed with water and recrystallized from isopropanol. The resulting material is taken up in chloroform, the solution treated with charcoal, filtered, concentrated to dryness under reduced pressure and recrystallized from isopropanol to afford pure d,l-1-[4-(4-chloro-

benzyloxy)-phenyl]-2-(3,3-diphenyl-3-hydroxypropylamino)propane melting at 125—127°.

The starting material is obtained as follows: A mixture of 30.4 g of 1-[4-(4-chlorobenzyloxy)-phenyl]-2-nitropropene (intermediate in Example 2), 80 g of iron powder, 3.2 g of ferric chloride, 40 ml of concentrated hydrochloric acid, 400 ml of ethanol and 1200 ml of water is stirred vigorously at reflux for ten hours, cooled and then filtered. The precipitate is extracted with methanol and the filtrate and extracts are combined and concentrated to dryness at reduced pressure. The residual solid is dissolved in hot isopropanol, the solution treated with charcoal, filtered and the filtrate refrigerated. The precipitate is collected, washed with petroleum ether and dried to afford 4-(4-chlorobenzyloxy)-phenylacetone melting at 76—80°.

Example 6

The mixture of 16 g of 1 - 1 - (4 - hydroxyphenyl) - 2 - (3,3 - diphenylpropylamino) - propane hydrochloride, 50 ml of dimethylsulfoxide and 3.4 g of sodium hydroxide in 10 ml of water is stirred at 60° for 1 hour, whereupon 7.2 g of 4-chlorobenzyl chloride are added and the whole is stirred over night at room temperature. The mixture is poured into 300 ml of N-aqueous sodium hydroxide solution, extracted with methylene chloride, the extract dried and evaporated. The residue is dissolved in 250 ml of ethyl acetate, the solution combined with that of 7 g of maleic acid in 25 ml of methanol, the mixture stirred for 1 hour and filtered, to yield the l - 1 - [4 - (4 - chlorobenzyloxy) - phenyl] - 2 - (3,3 - diphenylpropylamino) - propane maleate melting at 177—178°, $[M]_D = -58.1°$ (5% in methanol).

The starting material is prepared as follows: The mixture of 23 g of l-1-(4-hydroxyphenyl)-2-aminopropane, 31.2 g of 3,3-diphenylacrolein, 150 ml of anhydrous ethanol and 4 g of 10% palladium on charcoal is hydrogenated at 3.3 atm. for 6 hours. It is filtered, the filtrate evaporated, the residue dissolved in 400 ml of isopropanol and the solution combined with 12.5 ml of concentrated hydrochloric acid. After standing overnight the precipitate is collected and washed with isopropanol and diethyl ether, to yield the l - 1 - (4 - hydroxyphenyl) - 2 - (3,3 - diphenylpropylamino) - propane hydrochloride melting at 244—247°; $[M]_D = -35.1°$ (5% in methanol).

Analogously its dextrorotatory antipode is obtained, melting at 244—246°; $[M]_D = +31.9°$ (5% in methanol), which is converted as shown above into the d - 1 - [4 - (4 - chlorobenzyloxy) - phenyl] - 2 - (3,3 - diphenylpropylamino) - propane maleate melting at 176—178°, $[M]_D = +57.3°$ (5% in methanol).

Example 7

The mixture of 11.85 g of 1-(4-hydroxyphenyl)-3-(3,3-diphenylpropylamino)-butane (U.S.P. 3,262,977), 50 ml of dimethylsulfoxide and 3.1 ml of 10 N-aqueous sodium hydroxide solution is stirred at 80° for 1/2 hour, whereupon 5.1 g of 4-chlorobenzyl chloride are added and the whole is stirred for 8 hours while allowing to cool to room temperature. The mixture is poured into 600 ml of ice-cold N-aqueous sodium hydroxide solution, extracted with a total of 700 ml of ethyl acetate, the extract washed with saturated aqueous sodium chloride solution, dried and evaporated. The residue is taken up in the minimum amount of anhydrous ethanol, the solution combined with that of 3.48 g of maleic acid in ethanol, cooled and the precipitate collected, to yield the 1 - [4 - (4 - chlorobenzyloxy) - phenyl] - 3 - (3,3 - diphenylpropylamino) - butane maleate melting at 154—156°.

Example 8

The mixture of 17.3 g of 1-(3-hydroxyphenyl)-2-(3,3-diphenylpropylamino)-propane, 100 ml of dimethylsulfoxide and 5 ml of 10 N-aqueous sodium hydroxide solution is stirred at room temperature for 1/2 hour, combined with 8.05 g of 4-chlorobenzyl chloride and stirred 16 hours longer. It is poured into water, extracted with ethyl acetate, the extract washed with saturated aqueous sodium chloride solution, dried and evaporated. The residue is taken up in diethyl ether, the solution acidified with isopropanolic hydrogen chloride, the precipitate collected and washed with diethyl ether, to yield the 1 - [3 - (4 - chlorobenzyloxy) - phenyl] - 2 - (3,3 - diphenylpropylamino) - propane hydrochloride melting at 184—189°.

Analogously the 1 - [3 - (2 - chlorobenzyloxy) - phenyl] - 2 - (3,3 - diphenylpropylamino) - propane hydrochloride is prepared melting at 165—167°; as well as the 1 - [2 - (3 - chlorobenzyloxy) - phenyl] - 2 - (3,3 - diphenylpropylamino) - propane hydrochloride, melting at 144—145°.

The starting material is prepared as follows: The mixture of 100 g of m-methoxyphenylacetone, 129 g of 3,3-diphenylpropylamine and 500 ml of anhydrous

ethanol is refluxed for 2 hours, cooled to 20° and the solution of 95 g of sodium borohydride in 300 ml of water is added dropwise while stirring at room temperature. After stirring overnight the mixture is poured into water, extracted with methylene chloride, the extract dried and evaporated. The residue is taken up in diethyl ether, the solution acidified with isopropanolic hydrogen chloride and the precipitate collected, to yield the 1-(3-methoxyphenyl)-2-(3,3-diphenylpropylamino)-propane hydrochloride melting at 95—98°.

The mixture of 145 g of 1 - (3 - methoxyphenyl) - 2 - (3,3 - diphenylpropylamino) - propane hydrochloride and 1500 ml of 48% hydrobromic acid is refluxed for 45 minutes and allowed to stand at room temperature overnight. It is poured onto 4000 g of ice and 1000 ml of concentrated ammonium hydroxide, the mixture extracted with methylene chloride, the extract dried, evaporated and the residue recrystallized from ethyl acetate, to yield the 1 - (3 - hydroxyphenyl) - 2 - (3,3 - diphenylpropylamino) - propane melting at 122—124°.

Reacting the (3-methoxy-4-hydroxyphenyl)-acetone with the 3,3-diphenylpropylamine, reducing the resulting Schiff's base as shown above and reacting the resulting saturated compound with 3-trifluoromethylbenzyl chloride, the 1 - [3 - methoxy - 4 - (3 - trifluoromethylbenzyloxy) - phenyl] - 2 - (3,3 - diphenylpropylamino) - propane hydrochloride is obtained, melting at 142 to 146° after recrystallization from isopropanol.

Example 9

The mixture of 7.18 g of 1 - (3 - methyl - 4 - hydroxyphenyl) - 2 - (3,3 - diphenylpropylamino) - propane, 50 ml of dimethylsulfoxide and 2 ml of 10 N-aqueous sodium hydroxide solution is stirred for 1 hour at 60°. After cooling to room temperature 3.32 g of 4-chlorobenzyl chloride are added and the mixture stirred overnight at said temperature. It is poured into water, extracted with ethyl acetate, the extract dried and evaporated. The residue is taken up in isopropanol, the solution acidified with isopropanolic hydrogen chloride, the precipitate collected and washed with diethyl ether, to yield the 1 - [3 - methyl - 4 - (4 - chlorobenzyloxy) - phenyl] - 2 - (3,3 - diphenylpropylamino) - propane hydrochloride melting at 166—168°.

Analogously the 1 - [3 - fluoro - 4 - (4 - chlorobenzyloxy) - phenyl] - 2 - (3,3 - diphenylpropylamino) - propane hydrochloride is obtained, melting at 183—187°.

The starting material is prepared at follows: The mixture of 100 g of 3-methyl-4-methoxybenzaldehyde, 300 ml of nitroethane and 52 g of ammonium acetate is refluxed for 4 hours and evaporated, to yield the 1-(3-methyl-4-methoxyphenyl)-2-nitropropene.

The solution of 185.9 g of 1 - (3 - methyl - 4 - methoxyphenyl) - 2 - nitropropene in 500 ml of tetrahydrofuran is added dropwise to the slurry of 76 g of lithium aluminium hydride in 250 ml of tetrahydrofuran while stirring and cooling with ice-sodium chloride, and stirring is continued overnight at room temperature under nitrogen. The mixture is slowly combined with 300 ml of saturated aqueous ammonium chloride solution, diluted with 2000 ml of diethyl ether to facilitate stirring and filtered. The residue is washed with a total of 1500 ml of diethyl ether, the filtrate washed with saturated aqueous sodium chloride solution, dried and evaporated. The residue is taken up in diethyl ether, the solution acidified with ethanolic hydrogen chloride and the precipitate collected, to yield the 1-(3-methyl-4-methoxyphenyl)-2-aminopropane hydrochloride melting at 200—205°.

19.7 g of 1-(3-methyl-4-methoxyphenyl)-2-aminopropane hydrochloride are added to the solution of 4.93 g of sodium methoxide in 300 ml of anhydrous ethanol while stirring. After a few minutes the mixture is filtered, the filtrate evaporated and the residue taken up in 500 ml of benzene. The solution is combined with 19.01 g of 3,3-diphenylacrolein, refluxed for 2 1/2 hours on a water trap and evaporated. The residue is taken up in 250 ml of tetrahydrofuran, the solution combined with 14 g of lithium aluminium hydride and the mixture refluxed for 60 hours while stirring under nitrogen. It is combined with 250 ml of saturated aqueous ammonium chloride solution, filtered, the residue washed with diethyl ether and ethyl acetate. The filtrate is washed with saturated aqueous sodium chloride solution, dried and evaporated. The residue is taken up in diethyl ether, the solution neutralized with ethanolic hydrogen chloride and the precipitate recrystallized from isopropanol, to yield the 1 - (3 - methyl - 4 - methoxyphenyl) - 2 - (3,3 - diphenylpropylamino) - propane hydrochloride melting at 174—179°.

The mixture of 20.5 g of 1 - (3 - methyl - 4 - methoxyphenyl) - 2 - (3,3 - diphenylpropylamino) - propane hydrochloride, 100 ml of methylene chloride and 50 g of boron tribromide is stirred at 0° for 9 hours and at room temperature for 9 hours. It is evaporated, the residue poured onto ice and saturated ammonium hydroxide,

the mixture filtered and the precipitate recrystallized from benzene, to yield the 1 - (3 - methyl - 4 - hydroxyphenyl) - 2 - (3,3 - diphenylpropylamino) - propane melting at 115—118°.

The similarly prepared 1 - (3 - fluoro - 4 - hydroxyphenyl) - 2 - (3,3 - diphenylpropylamino) - propane melts at 186—188° after recrystallization from methyl Cellosolve. ("Cellosolve" is a Trade Mark.)

Example 10

According to the methods illustrated by the previous examples, preferably according to those mentioned under item 3) herein, the following racemic products are prepared from equivalent amounts of the corresponding starting materials:

1) 1 - [4 - (4 - fluorobenzyloxy) - phenyl] - 2 - (3,3 - diphenylpropylamino) - propane maleate, m.p. 161—163°;

2) 1 - [4 - (pentafluorobenzyloxy) - phenyl] - 2 - (3,3 - diphenylpropylamino) - propane maleate, m.p. 156—158°;

3) 1 - [4 - (4 - chlorobenzyloxy) - phenyl] - 2 - (3,3 - diphenylpropylamino) - propane maleate, m.p. 183—184°;

4) 1 - [4 - (4 - bromobenzyloxy) - phenyl] - 2 - (3,3 - diphenylpropylamino) - propane maleate, m.p. 183—185°;

5) 1 - [4 - (3 - trifluoromethylbenzyloxy) - phenyl] - 2 - (3,3 - diphenylpropylamino) - propane maleate, m.p. 135—137°;

6) 1 - [4 - (4 - cyanobenzyloxy) - phenyl] - 2 - (3,3 - diphenylpropylamino) - propane maleate, m.p. 80—82°;

7) 1 - [4 - (4 - carbamoylbenzyloxy) - phenyl] - 2 - (3,3 - diphenylpropylamino) - propane maleate, m.p. 184—185°.

Example 11

The mixture of 4.8 g of 1 - [4 - (4 - carbamoylbenzyloxy) - phenyl] - 2 - (3,3 - diphenylpropylamino) - propane (prepared from the maleate of Example 10/7 by extracting the suspension thereof in 100 ml of N-aqueous sodium hydroxide solution with methylene chloride and evaporating the dried extract), 25 ml of ethanol, 10 ml of water and 5.6 g of potassium hydroxide is refluxed for 18 hours under nitrogen. It is concentrated, the concentrate diluted with 75 ml of water and acidified with 10 ml of concentrated hydrochloric acid. The precipitate is filtered, washed with water, dried and triturated with diethyl ether, to yield the 1 - [4 - (4 - carboxybenzyloxy) - phenyl] - 2 - (3,3 - diphenylpropylamino) - propane hydrochloride melting at 188—190°.

Example 12

Preparation of 10,000 tablets each containing 50 mg of the active ingredient:

Formula:

1 - 1 - [4 - (4 - chlorobenzyloxy) - phenyl] - 2 - (3,3 - diphenylpropylamino) - propane maleate	500 g
Lactose	1,706 g
Corn starch	90 g
Polyethylene glycol 6,000	90 g
Talcum powder	90 g
Mamnesium stearate	24 g
Purified water	q.s.

Procedure:

All the powders are passed through a screen with openings of 0.6 mm. Then the drug substance, lactose, talcum, magnesium stearate and half of the starch are mixed in a suitable mixer. The other half of the starch is suspended in 45 ml of water and the suspension added to the boiling solution of the polyethylene glycol in 180 ml of water. The paste formed is added to the powders which are granulated, if necessary, with an additional amount of water. The granulate is dried overnight at 35°, broken on a screen with 1.2 mm openings and compressed into tablets using concave punches with 7.1 mm diameter, uppers bisected.

Preparation of 10,000 capsules each containing 100 mg of the active ingredient:

Formula:

d,l - 1 - [4 - (4 - chlorobenzyloxy) - phenyl] - 2 - (3,3 - diphenylpropylamino) - propane hydrochloride	1,000 g
Lactose	2,800 g
Talcum powder	200 g

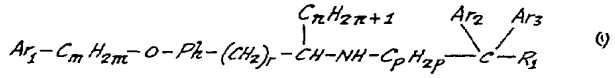
Procedure:

All the powders are passed through a screen with openings of 0.6 mm. Then the drug substance is placed in a suitable mixer and mixed first with the talcum, then with the lactose until homogenous No. I capsules are filled with 400 mg each, using a filling machine.

Analogously tablets and capsules are prepared from the remaining compounds illustrated by the previous examples.

WHAT WE CLAIM IS:—

1. A compound of the general formula I



(I)

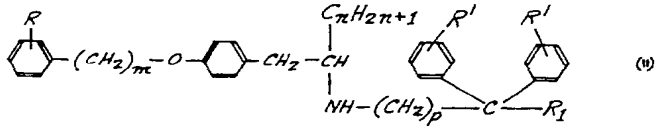
wherein Ar_1, Ar_2 and Ar_3, which may be the same or different, each represents an unsubstituted phenyl radical or a phenyl radical substituted by one or more substituents selected from halogen atoms and lower alkyl, lower alkoxy, trifluoromethyl, nitro, amino, mono-lower alkylamino, di-lower alkylamino, lower alkanoylamino, cyano, carboxy, carbo-lower alkoxy, carbamoyl, aminomethyl, mono-lower alkylaminomethyl and di-lower alkylaminomethyl groups, Ph represents an unsubstituted phenylyene radical or a phenylene radical substituted by one of the substituents listed for Ar_1, n is 0 or an integer from 1 to 4, m and p, which may be the same or different, each represents an integer from 1 to 4, r is the integer 1 or 2, and R_1 represents a hydrogen atom or a hydroxy group.

2. A compound of the general formula I as claimed in claim 1, in which Ar_1, Ar_2 and Ar_3, which may be the same or different, each represents an unsubstituted phenyl radical or a phenyl radical substituted by one or more substituents selected from halogen atoms and lower alkyl, lower alkoxy, trifluoromethyl, nitro, amino, mono-lower alkylamino or di-lower alkylamino, lower alkanoylamino, cyano, carboxy, carbo-lower alkoxy, aminomethyl, mono-lower alkylaminomethyl and di-lower alkylaminomethyl groups, Ph represents an unsubstituted 1,3- or 1,4-phenylene radical or such a phenylene radical substituted by one of the substituents listed for Ar_1, r is the integer 1, and the other symbols have the meanings given in claim 1.

3. A compound of the general formula I as claimed in claim 1, in which Ar_1, Ar_2 and Ar_3, which may be the same or different, each represents a phenyl, (lower alkyl)$_x$-phenyl, (lower alkoxy)$_x$-phenyl, (halogeno)$_x$-phenyl or (trifluoromethyl)-phenyl radical, Ph represents a 1,3- or 1,4-phenylene, (lower alkyl)-1,3- or 1,4-phenylene, (lower alkoxy)-1,3- or 1,4-phenylene, (halogeno)-1,3- or 1,4-phenylene or (trifluoromethyl)-1,3- or 1,4-phenylene radical, n is an integer from 1 to 4, each of m and p is an integer from 1 to 4, x is an integer from 1 to 5, r is the integer 1 or 2 and R_1 represents a hydrogen atom or a hydroxy group.

4. A compound of the general formula I is claimed in claim 1, in which r is the integer 1, and the other symbols have the meanings given in claim 3.

5. A compound of the general formula II



(II)

wherein each of R and R′ independently represents a hydrogen atom, a methyl or methoxy group, a fluorine, chlorine or bromine atom, or a trifluoromethyl group, m, n and p each represents the integer 1 or 2, and R_1 represents a hydrogen or hydroxy group.

6. A compound of the general formula II as claimed in claim 5, in which R_1, m, n and p have the meanings given in claim 5, R represents a chlorine atom, and R′ a hydrogen atom.

7. A compound of the general formula II is claimed in claim 5, in which R represents a chlorine atom in the meta- or para-position, each of R_1 and R′ represents a hydrogen atom, each of m and n the integer 1 and p the integer 2.

8. 1-[4-(3-Chlorobenzyloxy)-phenyl]-2-(3,3-diphenylpropylamino)-propane.

9. d,l-1-[4-(4-Chlorobenzyloxy)-phenyl]-2-(3,3-diphenylpropylamino)-propane.

10. 1-[4-(3,4-Dichlorobenzyloxy)-phenyl]-2-(3,3-diphenylpropylamino)-propane.

11. 1-[4-(4-Cyanobenzyloxy)-phenyl]-2-(3,3-diphenylpropylamino)-propane.

12. 1 - [4 - (4 - Chlorobenzyloxy) - phenyl] - 2 - (3,3 - diphenyl - 3 - hydroxy - propylamino) - propane.

13. l - 1 - [4 - (4 - Chlorobenzyloxy) - phenyl] - 2 - (3,3 - diphenylpropylamino) - propane.

14. d - 1 - [4 - (4 - Chlorobenzyloxy) - phenyl] - 2 - (3,3 - diphenylpropylamino) - propane.

15. 1 - [4 - (4 - Chlorobenzyloxy) - phenyl] - 3 - (3,3 - diphenylpropylamino) - butane.

16. 1 - [3 - (4 - Chlorobenzyloxy) - phenyl] - 2 - (3,3 - diphenylpropylamino) - propane.

17. 1 - [3 - (2 - Chlorobenzyloxy) - phenyl] - 2 - (3,3 - diphenylpropylamino - propane.

18. 1 - [2 - (3 - Chlorobenzyloxy) - phenyl] - 2 - (3,3 - diphenylproplyamino - propane.

19. 1 - [3 - Methoxy - 4 - (3 - trifluoromethyl - benzyloxy) - phenyl] - 2 - (3,3 - diphenylpropylamino) - propane.

20. 1 - [3 - Methyl - 4 - (4 - chlorobenzyloxy) - phenyl] - 2 - (3,3 - diphenylpropylamino) - propane.

21. 1 - [3 - Fluoro - 4 - (4 - chlorobenzyloxy) - phenyl] - 2 - (3,3 - diphenylpropylamino) - propane.

22. 1 - [4 - (4 - Fluorobenzyloxy) - phenyl] - 2 - (3,3 - diphenylpropylamino) - propane.

23. 1 - [4 - (Pentafluorobenzyloxy) - phenyl] - 2 - (3,3 - diphenylpropylamino) - propane.

24. 1 - [4 - (4 - Bromobenzyloxy) - phenyl] - 2 - (3,3 - diphenylpropylamino) - propane.

25. 1 - [4 - (3 - Trifluoromethyl - benzyloxy) - phenyl] - 2 - (3,3 - diphenylpropylamino) - propane.

26. 1 - [4 - (4 - Carbamoylbenzyloxy) - phenyl] - 2 - (3,3 - diphenylpropylamino) - propane.

27. 1 - [4 - (4 - Carboxybenzyloxy) - phenyl] - 2 - (3,3 - diphenylpropylamino) - propane.

28. The levorotatory optical antipole of a compound claimed in claims 1 to 8, 10 to 12 and 15 to 27.

29. The dextrorotatory optical antipode of a compound claimed in claims 1 to 8, 10 to 12 and 15 to 27.

30. A compound as claimed in any one of claims 1, 3, 7 and 13 to 29 in the form of a salt.

31. A compound as claimed in any one of claims 1, 3, 7 and 13 to 29 in the form of a physiologically tolerable salt.

32. A compound as claimed in any one of claims 2, 4 to 6 and 8 to 12 in the form of a salt.

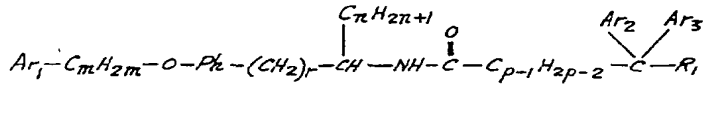
33. A compound as claimed in any one of claims 2, 4 to 6 and 8 to 12 in the form of a physiologically tolerable salt.

34. A pharmaceutical preparation which comprises a compound as claimed in any one of claims 1, 3, 7, 13 to 29 and 31 in admixture or conjunction with a pharmaceutically suitable carrier.

35. A pharmaceutical preparation which comprises a compound as claimed in any one of claims 2, 4 to 6, 8 to 12 and 33 in admixture or conjunction with a pharmaceutically suitable carrier.

36. A process for the manufacture of a 1-(aralkoxyphenyl)-2- or -3-(bis-arylalkylamino)-alkane of the general formula I as claimed in claim 1, which comprises

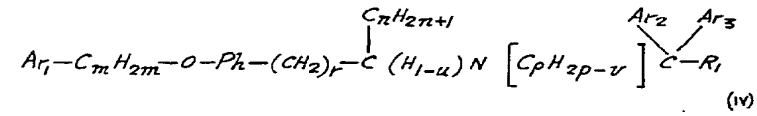
1) reducing a compound of the general formula III



(III)

or

2) reducing a compound of formula IV



(IV)

wherein u is 1, v is 0 and the other symbols have the meaning given above, or u is 0, v is 1 or 3 and the other symbols have the meaning given in claim 1, or

3) condensing a compound of the general formula V

$$Ar_1—C_mH_{2m}—T \qquad (V)$$

wherein T represents a reactive esterified hydroxy group and Ar and m are as defined in claim 1, with a compound of the general formula VI

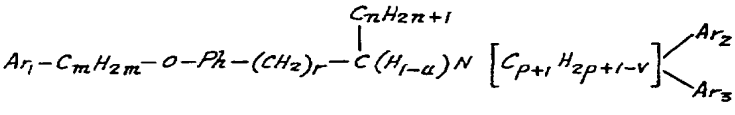
$$HO—Ph—(CH_2)_r—CH(C_nH_{2n+1})—NH—C_pH_{2p}—CR_1(Ar_2Ar_3) \qquad (VI)$$

in which the symbols are as defined in claim 1, or a reactive salt thereof, and, if desired, converting any resulting compound of formula I into another compound of formula I, and/or, if desired, converting a resulting free compound into a salt or a resulting salt into the free compound or into another salt, and/or, if desired, resolving a mixture of isomers or racemates obtained into the single isomers or racemates, and/or, if desired, resolving a racemate obtained into the optical antipodes.

37. A process as claimed in claim 36, wherein in reaction 1) the reduction of the amide is performed with a simple or complex light metal hydride.

38. A process as claimed in claim 36, wherein the reduction in reaction 2) is carried out with catalytically activated hydrogen, with nascent hydrogen or with a simple or complex light metal hydride.

39. A process as claimed in claim 36 or claim 38, wherein in reaction 2), to obtain a compound of formula I in which R_1 represents a hydrogen atom, there is used a starting material of the formula IVa



(IVa)

wherein all the symbols have the meanings given in claim 36.

40. A process according to claim 36, wherein in reaction 3) there is used a compound of formula V in which the reactive esterified hydroxy group is derived from hydrochloric acid.

41. A process according to claim 36 or claim 40, wherein the condensation of the compounds of formulae V and VI is carried out in the presence of a condensing agent.

42. A process according to any one of claims 36 to 41, wherein the levorotatory antipode of the resulting compound of formula I is isolated.

43. A process according to any one of claims 36 to 41, wherein the dextrorotatory antipode of the resulting compound of formula I is isolated.

44. A process as claimed in claim 36 carried out substantially as described in any one of Examples 6 to 11.

45. A compound of formula I as claimed in claim 1, whenever prepared by a process according to any one of claims 36 to 44.

46. A compound of the general formula I as claimed in claim 1, substantially as described in any one of Examples 6 to 11.

47. A process according to claim 36 for the manufacture of a compound of the general formula I given in claim 1, in which formula Ar_1, Ar_2 and Ar_3, which may

be the same or different, each represents an unsubstituted phenyl radical or a phenyl radical substituted by one or more than one substituent selected from halogen atoms, lower alkyl, lower alkoxy, trifluoromethyl, nitro, amino, mono-lower alkylamino, di-lower alkylamino, lower alkanoylamino, cyano, carboxy, carbo-lower alkoxy, amino-methyl, mono-lower alkylaminomethyl and di-lower alkylaminomethyl radicals, Ph represents an unsubstituted 1,3- or 1,4-phenylene radical or such a phenylene radical substituted by one of the substituents listed for Ar_1, r is the integer 1, and the other symbols have the meanings given in claim 36, or a salt thereof, which comprises

1) reducing a compound of the general formula III given in claim 36, in which formula r represents the integer 1, and the other symbols have the meanings given above, or

2) reducing a compound of the formula IV given in claim 36, in which formula r is the integer 1, Ar_1, Ar_2, Ar_3 and Ph have the meanings given above, and the other symbols have the meanings given in claim 36, or

3) condensing a compound of the formula V given in claim 36 with a compound of the formula VI shown in claim 36, in which formulae Ar_1, Ar_2, Ar_3 and Ph have the meanings given above, r is the integer 1, and the other symbols have the meanings given in claim 36, and, if desired, converting a resulting compound of formula I into another compound of formula I and/or, if desired, converting a resulting free compound into a salt or a resulting salt into the free compound or into another salt, and/or, if desired, resolving a mixture of isomers or racemates obtained into the single isomers or racemates, and/or, if desired, resolving a racemate obtained into the optical antipodes.

48. A process as claimed in claim 47, wherein in reaction 1) the reduction is performed with a simple or complex light metal hydride.

49. A process as claimed in claim 47, wherein the reduction in reaction 2) is carried out with catalytically activated hydrogen, with nascent hydrogen or with a simple or complex light metal hydride.

50. A process as claimed in claim 47 or claim 49, wherein in reaction 2), to obtain a compound of formula I in which R_1 represents a hydrogen atom, there is used a starting material of the formula IVa shown in claim 39, in which formula all the symbols have the meanings given in claim 47.

51. A process according to claim 47, wherein in reaction 3) there is used a compound of formula III in which a reactive esterified hydroxy group is derived from hydrochloric acid.

52. A process according to claim 47 or claim 51, wherein the reaction 3) is carried out in the presence of a condensing agent.

53. A process as claimed in claim 47 carried out substantially as described in any one of Examples 1 to 5.

54. A compound of formula I as defined in claim 47, whenever prepared according to the process claimed in any one of claims 47 to 53.

55. A compound of the formula I as defined in claim 47, substantially as described in any one of Examples 1 to 5.

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